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17 February 2005

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PODOPHYLLOTOXIN DERIVATIVES AS IGF-1R INHIBITORS

(57) Abstract: The invention refers to new compounds, e.g. podophyllotoxin derivatives, as well as to the use thereof and of known compounds as specific inhibitors of the insulin-like growth factor-1 receptor (IGF-1R). Said compounds can be used for treatment of IGF-1/IGF-1R dependent diseases, such as cancer, psoriasis, arteriosclerosis, certain endocrine and metabolic disorders etc.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D493/04, C07D317/48, C07D493/14, C07D491/153, C07C49/213, A61K31/343, A61K31/121, A61K31/36, A61K31/4355, A61K31/353, A61P5/06, A61P9/10, A61P17/06, A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, C07C, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEM ABS DATA, EPO-INTERNAL, WPI DATA, BIOSIS, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02102804 A1 (KAROLINSKA INNOVATIONS AB), 27 December 2002 (27.12.2002) --	1-16
X	WO 02102805 A1 (KAROLINSKA INNOVATIONS AB), 27 December 2002 (27.12.2002) --	1-16
X	J. Med. Chem., Vol. 44, 2001, Anne Dantzig et al: "Cytotoxic Responses to Aromatic Ring and Configurational Variations in alpha-Conidendrin, Podophyllotoxin, and Sikkimotoxin Derivatives", sid 180 - sid 185 --	10-11

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 October 2004	14 -10- 2004
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Per Renström/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (January 2004)

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J. Med. Chem., Vol. 39, 1996, Tameo Iwasaki et al: "Novel Selective PDE IV Inhibitors as Antiasthmatic Agents. Synthesis and Biological Activities of a Series of 1-Aryl-2,3-bis(hydroxymethyl)naphthalene Lignans", sid 2696 - sid 2704	10-11
X	STN International, File CAPLUS, CAPLUS accession no. 2002:298301, Document no. 137:185295, Basavaraju, Y. B. et al: "Synthesis of analogues of podophyllotoxin: Tetralones as intermediates for the synthesis of analogues of Beta-apopicropodophyllin"; & Indian Journal of Heterocyclic Chemistry (2002), 11(3), 229-232	8
X	STN International, File CAPLUS, CAPLUS accession no. 1967:411054, Document no. 67:11054, Swan, R. J. et al: "Optical rotatory dispersion studies. XLI. The absolute configuration of plicatic acid"; & Canadian Journal of Chemistry (1967), 45(3), 319-24	8
X	STN International, File CAPLUS, CAPLUS accession no. 1963:461993, Document no. 59:61993, Schreier, E.: "Natural products inhibiting mitoses. XI. Structure of sikkimotoxin. 1. Synthesis of stereoisomeric 6,7-dimethoxy analogs of podophyllotoxin"; & Helvetica Chimica Acta (1963), 46, 75-117	8
X	STN International, File CAOLD, CAOLD accession no. CA65:2187d, Braun, Loren L. et al: "2-(2-carboxyethyl)amino-1,4-naphthoquinone derivs"	8

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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-7 and 15-16
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☒ Claims Nos.: 1-6, 8-16
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

see next sheet

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see next sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

See next sheet

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

Box I.1.
Claims 1-7 and 15-16 relate to methods of treatment of the human or animal body by therapy or diagnostic methods practised on the human or animal body (PCT Rule 39.1(iv)). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds or compositions.

Box I.2.
Present claims 1-6 and 8-16 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found for only a very small proportion of the compounds. The present claims are also so wide that a meaningful search over their whole scope is impossible. The search has therefore been carried out for those parts of the claims which appear to be supported and disclosed, namely the following:

the parts of claims 1-6 and 12-16 relating to those compounds of formula IV in claim 6 that have oxygen substituents (e.g.-O-alkyl) in positions R_4, R_5 and R_{10},

the parts of claims 1-6 and 8-16 relating to those compounds of formula III in claim 8 for which R_4 and R_5 (same or different) are hydroxy or methoxy and for which R_9, R_{10} and R_{11} is methoxy,

the parts of claims 1-6 and 8-16 relating to those compounds of formula I in claim 10 for which R_4 and R_5 (same or different) are hydroxy or methoxy and for which R_9, R_{10} and R_{11} are methoxy,

the parts of claims 1-6 and 8-16 relating to derivatives of podophyllotoxin which derivatives only differ from podophyllotoxin in that the methylenedioxy group is exchanged for R_4 and R_5 (same or different) = hydroxy, methoxy, ethoxy, propoxy or isopropoxy, in that the methoxy groups on the free benzene ring may be exchanged for any oxyen substituents including -O-alkyl and bridges such as methylenedioxy groups, and in that R_{17} and R_{18} may only be hydrogen or hydroxy.

Furthermore, present claims 1-6 and 12-14 relate to methods and uses defined by reference to a desirable characteristic or property, namely inhibition of tyrosine phosphorylation of the insulin-like growth factor-1 receptor. In their present wording the claims may relate to a large number of different disorders which are not clearly defined by the fact that they might be treated by inhibition of said receptor. The claims do not meet the requirements of Article 6 PCT that claims shall be clear and concise.

.../...

Lack of Unity (Box II):

The International Search Authority considers that there are 2 inventions covered by the claims, indicated as follows:

1) The parts of claims 1-16 directed to derivatives of the compounds in WO02102804 and WO02102805 in which derivatives the methylenedioxy group corresponding to R_4 and R_5 is opened or exchanged for another functionality, which parts are represented by the example 4,5-demethylene-deoxypodophyllotoxin (Figure 2) and Compounds IA (Figure 3), Compounds IIIA and IIIC (Figure 5) and Compounds IVA, IVC and IVE (Figure 6).

2) The parts of claims 1-16 directed to derivatives of the compounds in WO02102804 and WO02102805 which derivatives are substituted on the benzene ring in the position corresponding to R_7 (such as Compounds IB, IC and ID in Figure 3), on the carbon between the rings in the position corresponding to R_1 and/or R_2 (such as Compounds IE and IF in Figure 3) or in both of these positions (such as Compounds IIA-IIF in Figure 4; Compounds IIIB and IIID-IIIF in Figure 5; Compounds IVB, IVD and IV *F* in Figure 6 and the picropodophyllin- and picropeltatin derivatives in Figure 7).

The ISA has carried out a partial search which relates to invention 1 mentioned above.

The present application has been considered to contain 2 inventions which are not linked such that they form a single general inventive concept, as required by Rules 13.1, 13.2 and 13.3 PCT, for the following reasons:

Both inventions relate to the problem of providing alternative, selective IGF-1R-inhibitors to the ones known from WO02102804 and WO02102805. Invention 1 solves this problem by exchange or opening of the methylenedioxy group that is characteristic for the podophyllotoxin derivatives. Invention 2 solves the problem by modification of the known podophyllotoxin derivatives in the part of the molecule consisting of the second ring in the naphtalene moiety, attached to the methylenedioxybenzene ring through R_7 and to the methylene bridge between the methylenedioxybenzene ring and the free (trimethoxy-)benzene ring through R_1/R_2.

.../...

Since the solutions are technically different, no single general concept can be formulated based on the technical features of the inventions. Consequently, the requirements of Rule 13.1 PCT are not met. It was investigated under Rule 13.2 if any further features, either in the claims or derivable from the description, could be considered as a same or corresponding feature and which could be considered a special technical feature establishing a technical link between the two groups of inventions. However, no such features were identified.

INTERNATIONAL SEARCH REPORT

Information on patent family members

03/09/2004

International application No.
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WO	02102804	A1	27/12/2002	AU	9446001	A 15/04/2002
				CA	2424931	A 11/04/2002
				CA	2451047	A 27/12/2002
				EP	1325035	A 09/07/2003
				EP	1397368	A 17/03/2004
				EP	1397369	A 17/03/2004
				NO	20035647	D 00/00/0000
				NO	20035648	D 00/00/0000
				SE	0102168	D 00/00/0000
				WO	02102805	A 27/12/2002
WO	02102805	A1	27/12/2002	AU	9446001	A 15/04/2002
				CA	2424931	A 11/04/2002
				CA	2451047	A 27/12/2002
				EP	1325035	A 09/07/2003
				EP	1397368	A 17/03/2004
				EP	1397369	A 17/03/2004
				NO	20035647	D 00/00/0000
				NO	20035648	D 00/00/0000
				SE	0102168	D 00/00/0000
				WO	02102804	A 27/12/2002